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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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QUESTION PRESENTED

Whether federal drug labeling laws preempt state-law tort claims that seek to hold drug manufacturers liable for using FDA-approved labeling.

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STATEMENT OF INTEREST[1]

The Generic Pharmaceutical Association ("GPhA") is a non-profit, voluntary association comprised of more than 140 manufacturers and distributors in the generic pharmaceutical industry, which in turn accounts for more than 63 percent of prescriptions dispensed in the United States each year. GPhA's members provide American consumers with safe and cost-effective medicines that are bioequivalent to, and have the same therapeutic value as, their brand-name counterparts. These products significantly improve public health while cutting annual healthcare costs by billions of dollars.

GPhA's members have a strong interest in preserving the Food and Drug Administration's exclusive authority over drug product labeling, and in the national uniformity that FDA's labeling pre-approval process provides. That is so not only because lay juries are especially ill-suited to second-guess FDA's expert labeling decisions, *see Riegel v. Medtronic*, 128 S.Ct. 999, 1008 (2008), but because allowing lay juries to impose disparate, state-specific labeling mandates through tort litigation threatens to subject drug manufacturers—and generic drug manufacturers *in particular*—to directly conflicting

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[1] All parties have consented to the filing of this brief, and letters evincing such consent have been filed with the Clerk. Pursuant to this Court's Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief and that neither such counsel, nor any party, nor any person or entity other than *amicus*, its members, or its counsel made a monetary contribution intended to fund the preparation or submission of this brief.

state and federal requirements. Indeed, federal law expressly requires each generic drug product to bear "the same" labeling FDA approved for use on that product's brand-name equivalent, so if lay juries nonetheless may require generic manufacturers to depart from the FDA-approved labeling—as one thinly-reasoned decision cited by the Vermont Supreme Court so held, *see* Pet. App. 12a (citing *Bell v. Lollar*, 791 N.E.2d 849, 855 (Ind. Ct. App. 2003))—it would be impossible for generic drug companies to comply with both their state and federal obligations.

That result is untenable, and GPhA's members have an obvious interest in seeing this Court restore the integrity and uniformity of the federal drug-labeling regime. GPhA respectfully asks this Court to reverse the Vermont Supreme Court's judgment.

SUMMARY OF THE ARGUMENT

GPhA fully supports the arguments that Wyeth makes in support of reversing the Vermont Supreme Court's decision. But whatever the merits of that decision may be with respect to the labeling rights and responsibilities of brand-name manufacturers like Wyeth, the case for federal preemption is even stronger with respect to state-law tort claims that challenge the sufficiency of FDA-approved labeling for generic drug products.

That is so because federal law expressly requires each generic drug product to bear "the same" labeling that FDA approved for use on the generic drug product's brand-name equivalent. 21 U.S.C. § 355(j)(2)(A)(v). As a result, FDA consistently has made clear that the labeling regulation on which the Vermont Supreme Court based its decision, 21 C.F.R. § 314.70(c)(6)(iii) (the "CBE regulation"), does not

apply to generic drug products at all, and that generic drug manufacturers categorically may not deviate from the FDA-approved labeling. *See, e.g.*, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 n.1 (proposed Jan. 16, 2008) (to be codified at 21 C.F.R. § 314) ("CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug.") (citations omitted).

With its sweeping declaration that FDA's labeling requirements merely "create a floor, not a ceiling, for state regulation," Pet. App. at 6, and unqualified assertion that "FDA approval of a drug label [is] but a first step in the process of warning consumers," *id.* at 15a, however, the Vermont Supreme Court's decision in this case threatens to subject generic drug manufacturers to directly conflicting state and federal requirements: either comply with federal law by replicating the label FDA's scientific experts approved for use on the generic drug's brand-name equivalent, and thereby risk potentially ruinous tort liability if a lay jury later takes issue with FDA's expert assessment of the label's sufficiency, or comply with the disparate labeling requirements imposed by lay juries in state-law tort litigation, and thereby risk potentially ruinous federal liability—including the withdrawal of FDA approval to market the drug, *see* 21 C.F.R. § 314.150(b)(10), and the imposition of sanctions for marketing a misbranded drug product. *See* 21 U.S.C. §§ 331, 333, 352.

That result cannot possibly be squared with the Supremacy Clause, and GPhA respectfully asks this Court to recognize that there is no lawful basis for allowing labeling-based state-law tort claims against generic drug manufacturers to proceed.

RELEVANT REGULATORY BACKGROUND

In order to promote the development, production, and marketing of affordable generic medicines, the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act ("Hatch-Waxman") establish an expedited FDA review process for proposed generic drugs and create significant incentives for generic manufacturers to enter the market. *See generally* 21 U.S.C. § 355(j) (2007); *see also Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 879 (D.C. Cir. 2004); *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988).

To that end, Hatch-Waxman allows FDA to approve proposed generic drug products without requiring their manufacturers to conduct the same kind of extensive investigational studies and clinical trials that must be performed before most brand-name drugs can be approved. *Cf.* 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d). Instead, FDA may approve a proposed generic drug without such studies if the generic drug's manufacturer can prove that its product is bio- and therapeutically equivalent to a brand-name drug that FDA previously determined to be safe and effective. 21 U.S.C. § 355(j)(2)(A).

Because the whole premise of Hatch-Waxman's streamlined review process for proposed generic drugs is that such drugs are indistinguishable from their brand-name counterparts, the statute naturally

seeks to ensure that the labeling on every generic drug product is indistinguishable from the labeling FDA approved for that product's brand-name equivalent. Each application for a proposed generic drug (or "ANDA") therefore must include "specimens of the labeling proposed to be used for [the generic] drug," *id.* § 355(j)(2)(A)(vi) (cross-referencing 21 U.S.C. § 355(b)(1)(F)); proof that "the conditions of use prescribed, recommended, or suggested in the labeling proposed for the [generic] drug have been previously approved for a [brand-name] drug," *id.* § 355(j)(2)(A)(i); and, most important, proof "that the labeling proposed for the [generic] drug is *the same* as the labeling approved for the [brand-name] drug ... except for changes required ... because the [generic] drug and the [brand-name] drug are produced or distributed by different manufacturers." *Id.* § 355(j)(2)(A)(v) (emphasis added). To implement that mandate, FDA's regulations in turn require generic applicants to submit a "side-by-side comparison of the[ir] proposed labeling [and] the approved labeling for the [brand-name] drug with all differences annotated and explained." 21 C.F.R. § 314.94(a)(8)(iv).

Despite Hatch-Waxman's expedited review process, years sometimes pass between the date an ANDA first is submitted to FDA and the date FDA approves it. Special problems thus arise when changes are made to a brand-name drug's labeling after an ANDA applicant first seeks marketing approval for a generic version of that drug—including interim labeling changes that brand manufacturers may effectuate without FDA pre-approval in extraordinary circumstances. *See* 21 C.F.R. § 314.70(c)(6)(iii).

In such cases, FDA consistently has required generic applicants to replicate the latest *FDA-approved* version of the brand-name drug's label—and flatly prohibits them from replicating any *unapproved* labeling that the brand manufacturer implemented through the CBE process, or otherwise adding new warnings not contained in the brand-name product's approved labeling. *See, e.g.*, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992); GPhA App. 13a-15a (Letter from Douglas L. Sporn, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to All ANDA and AADA Applicants (Dec. 24, 1996)); GPhA App. at 26a (Office of Generic Drugs, *Guidance For Industry: Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000)).

At the same time, FDA consistently has made clear that generic manufacturers, in marked contrast to their branded counterparts, are not entitled to use the CBE regulation to effectuate their own labeling changes without prior FDA approval. *See, e.g.*, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 n.1 (proposed Jan. 16, 2008) [the "CBE Interpretive Guidance"]; 57 Fed. Reg. 17950, 17953, 17961 (Apr. 28, 1992)); *see also* Br. of the United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, No. 05-CV-05500-MMB (E.D. Pa. filed May 10, 2006) [the "Colacicco Amicus Br."], at 6, *unpaginated full-text reproduction available at* 2006 WL 1724170.

Finally, federal law subjects generic companies to strict penalties for marketing drug products that

bear labeling which deviates from the labeling FDA approved for use on the brand-name equivalent. Hatch-Waxman itself prohibits FDA from approving an ANDA if "information submitted in the application is insufficient to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the [brand-name] drug referred to in the application." 21 U.S.C. § 355(j)(4)(G). In turn, FDA's implementing regulations authorize the withdrawal of a generic drug's approval if its labeling "is no longer consistent with that for the [brand-name] drug referred to in the [ANDA]." 21 C.F.R. § 314.150(b)(10). And whether or not manufacturers can continue to market a drug product with inconsistent labeling, generic companies may be subjected to draconian penalties for having marketed a "misbranded" drug product to consumers. 21 U.S.C. § 331 (liability for misbranding); 21 U.S.C. § 333 (penalties for misbranding); 21 U.S.C. § 352 (definition of misbranding); *see also* Colacicco Amicus Br. at 15 & n.6, 17.

ARGUMENT

Federal Drug Labeling Laws Preempt State-Law Tort Claims That Seek To Hold Drug Manufacturers Liable For Using FDA-Approved Labeling.

The Vermont Supreme Court erred by holding that federal drug labeling laws permit state-law tort claims that seek to hold drug manufacturers liable for using FDA-approved labeling. Federal law preempts state laws (including state-law causes of action) that "make it 'impossible' for private parties to comply with both state and federal law," *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873, 881

(2000), or which otherwise "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). Yet that is precisely what the Vermont Supreme Court's decision threatens to do. Plaintiffs are free to challenge FDA's prior labeling determinations or seek prospective product-labeling changes by lodging complaints directly with FDA, but federal law precludes them from doing so by bringing state-law tort claims in court.

The Vermont Supreme Court, however, asserted that federal law permits such claims to proceed because FDA's CBE regulation purportedly allows drug manufacturers to institute new labeling precautions "without prior FDA approval" and, thus, that "federal labeling requirements create a floor, not a ceiling, for state regulation." Pet. App. 6a; *see also id.* at 10a-11a ("[The CBE] regulation ... allows a drug's manufacturer to alter the drug's label without prior FDA approval when necessary.... While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [the CBE regulation thus] allows manufacturers to avoid state failure-to-warn claims without violating federal law."); *id.* at 15a ("[The CBE regulation] does not allow us to interpret FDA approval of a drug label as anything but a first step in the process of warning consumers. When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability."); *id.* at 23a ("Congress did not intend to

interfere with state prerogatives except where doing so is absolutely necessary, and the plain language of the [CBE] regulation makes such interference unnecessary here.") (internal cross-reference omitted).

As Wyeth well explains, those claims incorrectly characterize certain rights and responsibilities of brand manufacturers under the CBE regulation, and various aspects of FDA's role in regulating the labeling of brand-name drugs. *See, e.g.*, Wyeth Br. at 34-40. But whatever the merits of those claims may be with respect to the labeling of brand-name drug products, those claims are just plain wrong when it comes to the labeling rights and responsibilities of generic manufacturers and FDA's role in policing the labeling of generic drug products.

Federal law expressly mandates that the labeling on each generic drug product must be "the same" as the labeling FDA approved for use on the product's brand-name equivalent, 21 U.S.C. § 355(j)(2), and every other conceivable source of federal law either replicates or otherwise implements that plain statutory requirement. To that end, FDA's Hatch-Waxman regulations reiterate the statutory mandate and also require generic applicants to submit a side-by-side comparison of the brand-name and proposed generic labeling so that FDA can ensure that the respective product labels are substantively identical. 21 C.F.R. § 314.94(a)(8)(iv). Indeed, FDA flatly rejected a proposal at the time it adopted those regulations that would have allowed generic manufacturers "to deviate from the labeling for the [brand-name] drug to add contraindications, warnings, precautions, adverse reactions, and other

safety-related information," 57 Fed. Reg. at 17961—explaining both that Hatch-Waxman expressly requires each proposed generic drug "product's labeling [to] be the same as the [brand-name] drug product's labeling because the [brand-name] drug product is the basis for [generic drug product] approval," and that "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.*

Since that time, FDA repeatedly has warned generic applicants to conform their product labeling to the latest FDA-approved labeling for the brand-name equivalent—regardless of any interim, manufacturer-initiated changes to the brand-name product labeling. *See, e.g.*, GPhA App. 15a (warning that generic applicants should "NOT utilize the Physician's Desk Reference (PDR) as the source for the most recently approved labeling of the innovator's product," because "some of this labeling may have been ... implemented prior to FDA approval" and "*FDA must ... approve [such] labeling before it is acceptable for use as model labeling for an ANDA/AADA product*") (capitalization in original; emphasis added); *see also* GPhA App. 26a, 28a (explaining that "[t]he sponsor of an ANDA is ... responsible for ensuring that the labeling contained in its application is the same as the *currently approved* labeling of the [branded equivalent]," and instructing ANDA sponsors to "submit revised labeling" to FDA when "labeling changes [are] needed because of *approved changes* to the labeling of the [branded equivalent]") (emphasis added).

Perhaps most important, FDA long has made clear—and just recently reiterated—that generic drug manufacturers are not entitled to use the CBE regulation to effectuate unapproved product-labeling changes under any circumstances. *See, e.g.*, 73 Fed. Reg. at 2849 n.1 ("CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug."); *see also* Colacicco Amicus Br. at 6 ("For a generic drug manufacturer, there is no statutory or regulatory provision permitting the manufacturer to make a labeling change to its generic drug without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug."); *id.* at 17 ("[A] generic drug manufacturer is not permitted to add a warning or caution to the label without prior approval from FDA.") (citing 21 U.S.C. §§ 355(j)(2)(A)-(C); 21 C.F.R. § 314.150(b)(10)).

Regardless of whether the CBE regulation permits brand manufacturers to effectuate labeling changes without prior FDA approval, and without respect to the particular conditions under which they may (or may not) do so, it thus is beyond serious dispute that federal law flatly prohibits generic drug manufacturers from initiating their own labeling changes; adding new warnings without first securing FDA pre-authorization; or otherwise deviating from the latest labeling that FDA has approved for a given generic drug product's brand-name equivalent.

As a result, there is no conceivable basis for applying the Vermont Supreme Court's decision—

which hinged entirely on the conclusion that FDA's CBE regulation authorizes manufacturers to initiate labeling changes without FDA pre-approval, *see, e.g.*, Pet. App. 10a-11a, 15a, 23a—in cases involving state-law claims against generic manufacturers, for whom the CBE process is unavailable. Indeed, applying the state court's decision in such cases would subject generic companies to directly conflicting state and federal labeling requirements in clear violation of the Supremacy Clause.

If, on one hand, generic companies heed federal law by maintaining their FDA-approved labeling, they would risk significant monetary damages in state-law tort litigation that seeks to second-guess FDA's expert labeling determinations. *See* Pet. App. 12a (citing *Bell*, 791 N.E.2d at 855 (holding that generic manufacturers are subject to state-law tort liability despite Hatch-Waxman's explicit requirement that they use only FDA-approved labeling)). And if, on the other hand, generic manufacturers yield to the pressure of state-law tort litigation by modifying their labeling to meet state-law requirements, there is no question that they would face significant federal sanctions—including the revocation of FDA marketing approval, 21 C.F.R. § 314.150(b)(10), and (as FDA recently reiterated) the imposition of potentially draconian sanctions for marketing a misbranded product. *See, e.g.*, 21 U.S.C. §§ 331, 333, 352; Colacicco Amicus Br. at 15 & n.6, 17; *see also Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 537-38 (E.D. Pa. 2006) (rejecting claims that generic manufacturers can be subjected to state-law labeling suits due to conflict with federal law); *Conte v. Wyeth, Inc.*, No. CGC-04-437382, 2006 WL 2692469 (Cal. Super. Ct. Sept. 14, 2006) (same).

It goes without saying that the Supremacy Clause is designed precisely to prevent regulated parties from being forced to make such intolerable choices, and thus requires state interests to give way whenever their pursuit would conflict with federal mandates. *See, e.g., Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 108 (1992) ("[U]nder the Supremacy Clause, from which our pre-emption doctrine is derived, 'any state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'") (quoting *Felder v. Casey*, 487 U.S. 131, 138 (1988)); *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 143 (1963) ("[F]ederal exclusion of state law is inescapable ... where compliance with both federal and state regulations is a physical impossibility.").

That is precisely the case here, and GPhA thus respectfully asks this Court to overturn the Vermont Supreme Court's decision or otherwise make clear that the lower court's reasoning cannot be applied to state-law claims challenging the sufficiency of generic drug labeling.

CONCLUSION

For the foregoing reasons, the Vermont's Supreme Court's judgment should be reversed.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Rockville, MD 20857

DEC 24, 1996

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

As part of the ongoing initiatives to reinvent government, the Office of Generic Drugs (OGD), like most other Federal programs, is faced with reduced resources. In addition to diminishing resources, OGD experienced a significant increase in submissions in late 1995. This higher level of submissions has continued in 1996. These combined factors resulted in an increased backlog of pending submissions. In order to help minimize the impact of these factors on review times, OGD began a series of internal meetings to identify procedures that would help streamline the review process. In addition, OGD believes these efforts will improve communications with industry and reduce the overall time to approval of abbreviated applications.

This letter describes the first streamlining initiatives that affect the chemistry, bioequivalence and labeling review processes. OGD looks forward to implementing additional streamlining initiatives in the future. The letter also contains an update on a variety of application related matters that will be of interest to applicants.

The Office trusts the information will be useful to you. Your cooperation in these matters will assist us

in our effort to improve the efficiency of the generic drug review process.

Sincerely yours.

/s

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation
and Research

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REVIEW ISSUES

COMMUNICATING NOT APPROVABLE DETERMINATIONS

Effective January 1, 1997, the Office of Generic Drugs (OGD) will provide most application related "not approvable" deficiencies, both major and minor, to ANDA/AADA holders via facsimile for unapproved original applications. This is expected to decrease time to final action on applications. However, for the present time, the Division of Bioequivalence will continue to issue deficiency letters as it has always done.

The facsimile will include the usual components of a deficiency letter, but not in the traditional letter format. It will include:

A. A list of chemistry, manufacturing, and controls (CMC) deficiencies followed by additional CMC comments regarding status of methods validation, pre-approval inspection, and other related points.

B. A list of labeling deficiencies.

C. A list of microbiology deficiencies, if applicable.

A cover sheet will accompany the deficiency list which will provide instructions on how to respond to the facsimile.

To assist the Office in providing the facsimiles, applicants are requested to provide or update the facsimile number for its Regulatory Affairs contact person.

MAJOR NOT APPROVABLE DEFICIENCY PROCEDURES

Major CMC deficiencies identified by OGD will be sent to the applicant by facsimile. Responses from

the applicant to these deficiencies will be regarded as a major amendment and should be submitted as an archival (hard) copy to OGD. OGD will not accept facsimile responses for major deficiencies.

MINOR NOT APPROVABLE DEFICIENCY PROCEDURES

For CMC deficiencies defined as minor, OGD will also communicate to the applicant by facsimile. The facsimile cover sheet that OGD sends to an applicant will identify the deficiency response as either a "Facsimile Amendment" or a "Minor Amendment". Procedures for responding to these two types of amendments are as follows:

A. Facsimile Amendment

There will be some minor deficiencies for which OGD believes a complete response can be provided by the applicant within 30 days. These deficiencies will be provided by facsimile and will NOT stop the regulatory review clock.

The applicant will be asked to respond directly to OGD's document room by facsimile, followed with a hard copy. Facsimile amendments will be reviewed ahead of other priority of routine submissions pending in the reviewer's queue.

Should the complete response (facsimile and hard copy) not be received within 30 days, the applicant's response will be considered a minor amendment and placed into the reviewer's minor amendment queue.

B. Minor Amendment

There will be some minor amendments for which a response cannot be provided within

30 days. These will typically be for situations when the response is beyond the control of the applicant, *e.g.*, Drug Master File (DMF) deficiencies. OGD will provide these deficiencies by facsimile and will STOP the regulatory review clock. In addition, the applicant's response (minor amendment) should be submitted as an archival (hard) copy to OGD and will be placed into the reviewer's queue according to OGD's first-in, first-reviewed policy. OGD will not accept facsimile responses for these minor amendments.

In order to evaluate the expected benefits of this new process, the Office will be monitoring the impact on action times. However, reports of industry experiences with this process are encouraged.

PHONE CONSULTATION FOLLOWING SECOND REVIEW CYCLE WITH MAJOR DEFICIENCIES

Applicants who find that an application continues to have major CMC deficiencies after the second review cycle are encouraged to call the appropriate Project Manager (PM) in OGD to discuss or clarify the deficiencies. Where appropriate the PM will involve the chemistry reviewer and/or others in the discussion. The goal is to answer questions, assist the applicant to understand the identified deficiencies and, hopefully, eliminate further major deficiency reviews. In some cases meetings may be necessary to clarify these deficiencies. OGD will contact the applicant within approximately 30 days after issuance of the second major deficiency letter if the Office has not been contacted by the applicant. OGD will also use the same approach for subsequent reviews where major deficiencies remain.

Currently, OGD is unable to provide this level of service after the first review cycle due to the volume of such submissions and the Office's limited resources.

ALTERNATE DRUG SUBSTANCE FOR ORIGINAL APPLICATIONS

The Office of Generic Drugs has announced a change in policy regarding adding an alternate source of the new drug substance (NDS) to an original application prior to approval.

Previously, if an abbreviated application was otherwise approvable with the exception of an unsatisfactory inspection of current Good Manufacturing Practices (cGMP) for the primary NDS supplier used to manufacture the exhibit/bioequivalence batch, it would not be approved until those cGMP issues were resolved. In order to qualify an acceptable alternate source of the NDS, a new exhibit batch based on the alternate source would be needed. Additionally, a bioequivalence study would be required (depending on dosage form) to support use of the alternate source.

For unapproved applications, OGD now allows substitution of an alternate source of the new drug substance based on assurance that the specifications and test data are essentially the same as those of the original source used in the exhibit batch (and bioequivalence study, if required) that would have been acceptable except for cGMP issues, etc. Additionally, the DMF must be found acceptable. Generally, a new *in vivo* bioequivalence study will not be required for the alternative dissolution data depending on the dosage form of the proposed product. This new policy is identical to the existing

policy regarding post approval changes to provide for alternate sources of the NDS.

Note that there are some situations where this new policy would not apply and a new acceptable exhibit batch, and *in vivo* bioequivalence study, and comparative dissolution data would be required. This might be the case when there are significant differences in particle size of physicochemical characteristics.

BIOEQUIVALENCE ISSUES

ELECTRONIC SUBMISSION PROJECT

Effective January 1, 1997, the Office of Generic Drugs will implement its program for electronic submission of bioequivalence data. The program was developed under contract with the University of Maryland (UM). Under the program, applicants that choose to, may prepare electronic submissions on diskette with the aid of a user-friendly program call Entry and Validation Program (EVA). EVA is free of charge to applicants through the UM's World Wide Web site (http://mundos.ifsm.umbc.edu/-fdacom). The Web site also permits applicants to register as participants and to obtain updated information on he program including any new versions of EVA. Companies can also ask technical questions through the Web site, which will be addressed by UM staff.

The program is expected to have a very positive impact on the efficiency of reviews, ultimately reducing review times. In addition, it is hoped the program will help reduce the time required to reach approval. Therefore, OGD strongly encourages firms to participate.

For most companies, the time to start planning the electronic submission is before study data are

prepared. For those using Contract Research Organizations (CROs) to conduct bioequivalence studies, applicants could specify in their requirements that the CROs prepare the data in the requested format. CROs are encouraged to access the UM Web site and to become familiar with EVA and submission requirements. Applicants may also make electronic submissions for applications already submitted to the office, but should contact the Bioequivalence Project Manager (Ms. Lizzie Sanchez, 301-594-2290) first, to make certain the electronic submission will be received in time for the review.

We hope to conduct training for applicants in conjunction with UM. Those applicants interested in such training are encouraged to register their interest through the UM Web site. Technical questions about the program may be addressed to the UM at 410-455-3888 or through the UM Web site. Regulatory questions may be addressed to the Bioequivalence Project Manager.

The electronic submission program is part of a larger strategy for Electronic Regulatory Submission and Review (ERSR) which will soon include the chemistry, manufacturing, an controls (CMC) portion of generic drug applications.

AVAILABILITY OF BIOEQUIVALENCE PROTOCOL REVIEWS

Firms frequently submit proposed *in vivo* bioequivalence study protocols to OGD. Often these are duplicative of already submitted and reviewed protocols. In order to decrease the burden of reviewing several protocols for the same drug product, OGD is now making available copies of acceptable protocols and related review comments. OGD believes that by utilizing completed review

comments, firms will need to submit fewer protocols, freeing time for evaluation of applications. Copies may be obtained from the Drug Information Branch, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD, 20857. The current phone number for the Drug Information Branch is (301) 827-4573. Please note that this number was recently changed because that branch relocated.

The list of protocols available may be accessed through "FAX on Demand" at (800) 342-2722 or (301) 827-0577. You are encouraged to obtain an updated list by this means. However, the Division of Bioequivalence will also maintain a listing.

There are caveats to be borne in mind regarding this new resource:

A. The material available will be redacted protocols and letters transmitting the review comments.

B. It will take some time to prepare protocols and reviews for distribution through this process. Therefore, the number of different product protocols and review will gradually increase, over time.

C. The procedure is new and may require fine tuning. Thus, comments and suggestions are encouraged. These may be submitted to Ms. Lizzie Sanchez at (301) 594-2290.

D. There will be a transition period during which firms with pending requests for protocol review may be contacted regarding the imminent availability of a review of another protocol regarding the product for which they had submitted a protocol. The firm may wish

to withdraw its protocol and use information available from the previously acceptable review.

Please note that though this service is available, the Division may be contacted should there appear to be circumstances necessitating review of another protocol for the same drug product.

UPDATE ON ALBUTEROL INHALATION AEROSOL GUIDANCE

On January 27, 1994, OGD issued the guidance titled "Interim Guidance for Documentation of *in vivo* Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)." Since its publication, the Office has had the opportunity to review additional information on various aspects of *in vivo* and *in vitro* testing conducted as described in the guidance and has concluded that a revision of the guidance is needed. A CDER working group developed recommendations for revision and presented them to a joint session of the Advisory Committee for Pharmaceutical Science (ACPS) (a re-configuration of the Generic Drug Advisory Committee — GDAC) and the Pulmonary Drugs Advisory Committee in August of 1996.

Therefore, should studies for albuterol metered dose inhalers (MDIs) be under consideration, sponsors are strongly encouraged to wait for the revised-guidance, or, in the interim, discuss their planned study with the Division of Bioequivalence. The guidance will be developed as expeditiously as possible and the industry will be informed of its availability.

BIOEQUIVALENCE STUDIES TO BE CONDUCTED IN APPROPRIATE SUBJECTS

Though it is preferable to conduct bioequivalence testing in normal healthy volunteers, there are

certain products for which use in healthy persons might be an unacceptable risk.

A. Cytotoxic drugs

Certain conditions and considerations regarding bioequivalence studies of cytotoxic drugs need to be specified. Please note the following:

21 CFR 320.31(a)(3) requires that any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an investigational new drug application (IND). An IND provides assurance that studies proposed will have adequate safeguards for the safety of the subjects.

It is therefore recommended that studies with the following products be conducted in the appropriate patient population. Note also that the listing (developed in conjunction with the Division of Oncologic Drug Products) is subject to the updating and revision. Consultation with the Office is recommended if any questions arise.

Bisulfan	Chlorambucil
Cyclophosphamide	Etoposide
Hexamethylmelamine	Lomustine
Melphalan	Pipobroman
Procarbazine	Thioguanine
Uracil Mustard	Methoxsalen
Estramustine Phosphate	

B. Ipratroprium

In order to fully evaluate the bioequivalence of this product, studies should be conducted in the appropriate patient population.

IN VIVO STUDIES UNDER SUPAC-IR

Under the Center's Guidance for Industry: Immediate Release Solid Oral Dosage Forms (SUPAC-IR) there are two types of post-approval changes for which *in vivo* bioequivalence testing is requested: Level 3 changes in components and composition as well as Level 3 manufacturing process changes. For generic drugs, the *in vivo* bioequivalence test should always compare the product after a post-approval change against the reference listed drug. However, in instances when a bioequivalence study is not necessary, dissolution studies should compare the applicant's generic product after a post-approval change against the same product prior to the change.

If there are any questions in regard to a reference product, please contact the Division of Bioequivalence for advice.

LABELING REVIEW CHANGES

The abbreviated application regulations require that side-by-side labeling comparisons be included with the submission of the original, unapproved application, with all differences between the proposed ANDA/AADA and the reference listed drug (RLD) labeling annotated and fully explained [See 21 CFR 314.94(a)(8)]. Side-by-side comparisons enable reviewers to readily identify differences between the ANDA/AADA and the reference listed drug labeling and/or the previous version of the applicant's labels and labeling.

OGD is now requesting a side-by-side comparison for all labeling changes submitted, not only in original applications, but also for all amendments and supplements. This comparison will help reduce

the time required to review each new version of proposed labeling.

Additional actions to streamline the labeling review process have resulted in the following changes:

A. OGD will provide pen and ink comments directly on a applicant's proposed labeling and attach those comments to the Not Approvable facsimile. This will eliminate the time consuming task of identifying where in the labeling changes should be made and explaining the needed changes in letter format. This will conserve reviewer's time, thus making more efficient use of OGD resources.

B. Effective immediately, when changes are needed in labeling because of changes in the RLD labeling, OGD will either identify the specific changes to be made or will provide a copy of the most recently approved labeling of the RLD. In the past when MAJOR changes were required in the labeling, the applicant was required to obtain a copy of the cited approved labeling from the Freedom of Information (FOI) staff, then submit a supplement or amendment. This process added 4 to 6 weeks to the process of updating the ANDA/AADA labeling.

   Please note that OGD will NOT supply labeling of the RLD BEFORE an application is filed. The most recent APPROVED labeling should be obtained from the FOI staff prior to preparation and submission of the labeling in an ANDA/AADA.

The Division of Labeling and Program Support highly recommends that ANDA/AADA applicants NOT utilize the Physician's Desk Reference (PDR) as the source for the most recently approved labeling of the innovator's product. Although the PDR may represent labeling that is available in the marketplace, some of this labeling may have been submitted to the Agency as a "Special Supplement - Changes Being Effected" (SSCBE). As such, it would have been implemented prior to FDA approval in accordance with 21 CFR 314.70(c). The FDA must still review, possibly recommend changes and approve the labeling before it is acceptable for use as model labeling for an ANDA/AADA product. In addition, other changes may have been made in the approved labeling after the publication of the PDR.

APPLICATION PROCESS ISSUES

Refusal to File Issues

The Office evaluates abbreviated applications for completeness and acceptability prior to filing them for review. OGD has identified many issues which previously would have resulted in refuse [sic] to file determinations which can be easily resolved by applicants. These are now communicated by OGD by telephone rather than issuing a letter which can take weeks. Such items include:

No cGMP statement
FDA Form 356h does not contain an original signature
Improper patent certification
Exclusivity rights not addressed
No debarment/list of convictions statement
No certification of field copy
Need for additional copies of labeling

Applicants are given 10 working days to respond. If a response is not received in that time, a refuse to file letter is issued.

This approach has resulted in a decrease in refuse to file determinations and moves applications into the review queue more rapidly. Even with this approach, the refuse to file rate for applications remains high. Therefore, an update of the key reasons the Office refuses to file abbreviated applications follows:

A. DMF Issues

No authorization for the Drug Master File (DMF) or incomplete information about the DMF.

The DMF authorization must be from the DMF holder or its U.S. agent to permit the agency to refer to the DMF on behalf of the applicant. If the authorization is from the agent, an additional letter of appointment of the agent must also be included from the holder of the DMF (link to DMF holder). The authorization for the agency to refer to the DMF must reference the specific applicant, not another corporate entity related to the applicant.

For further information please refer to the CDER Guideline for Drug Master Files.

B. Inactive Ingredient Issues

Inadequate information on the characterization of inactive ingredients.

The regulations related to parenteral, ophthalmic, otic and topical dosage forms [21

CFR 314.94(a)(9)] state that applicants shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that the inactive ingredients do not affect the safety of the proposed drug product. Additionally, OGD's Interim Inactive Ingredients Policy dated November 17, 1994, address inactive ingredient issues in more detail. The Interim Inactive Ingredient Policy is available in the OGD Docket (No. 9050308).

Thus, applicants should demonstrate that the proposed drug product is qualitatively and quantitatively the same as the reference listed drug product for parenteral, ophthalmic, otic, and topical dosage forms. An applicant may seek approval of a drug product that differs from the RLD, in certain instances, as described in the regulations.

Generally, products for oral inhalation are considered topical products. Therefore, applicants for these products are requested to provide a qualitative and quantitative comparison. Please refer to the Interim Inactive Ingredient Policy for further guidance.

For other topical products, i.e., creams, lotions, gels, suspensions, and solutions an applicant is requested to provide the following information:

1. Qualitative Statement

   A list of ingredients (test drug and reference drug) to show a qualitative comparison.

2. Quantitative Statement

The quantitative composition of the test drug and the results of analysis of the reference drug. It may not be possible to accurately analyze some inactive ingredients contained in the reference product. However, applicants should make their best efforts to quantitatively analyze the ingredients in the reference drug and submit the results in the application. If an ingredient cannot be analyzed, or if results are irrelevant or inconclusive, an explanation should be provided. Sponsors may use the Center for Drug Evaluation and Research Inactive Ingredient Guide (IIG) as a reference for safe maximum levels. If the ingredient levels are not listed, the sponsor may also refer to other sources of information, such as other approved topical products where quantitative levels are known, recognized literature references or information from the ingredient manufacturer.

OGD does not require a quantitative or qualitative analysis beyond the normal analytical capabilities within the industry.

If applicants have questions regarding inactive ingredients, they may submit a request for the opinion of the OGD on the acceptability of inactive ingredients prior to the submission of an application. The Office can provide certain information in response to such requests.

C. Exclusivity Issues

Exclusivity right(s) or patent(s) not addressed.

Patents and exclusivity must be addressed. When there is no exclusivity or patent listed in the Orange Book, the applicant should provide a statement to this effect. It is also suggested that applicants verify they are using a current edition of the Orange Book and/or cumulative supplement as the basis for this information.

D. Packaging Information

No record of or incomplete packaging information on the exhibit batch.

This packaging information is requested in order for the application to be filed. This request is outlined in OGD's Policy and Procedure Guide #41-93.

ACCEPTANCE OF ANDA BASED ON A PENDING PETITION FOR A DETERMINATION OF REASONS FOR VOLUNTARY WITHDRAWAL OF THE REFERENCE LISTED DRUG

OGD can accept an Abbreviated New Drug Application that refers to a listed drug that has been voluntarily withdrawn from sales as long as the applicant provides evidence that a Citizen's Petition has been submitted to request a determination of whether a listed drug has been voluntarily withdrawn for safety or efficacy reasons. A Center response to that petition is not required for filing purposes. However, the Center must have made its determination on relisting prior to the approval of the ANDA. (See 21 CFR 314.161 and 314.122)

DOCUMENTATION OF APPROPRIATE AUTHORIZATION OF AGENTS

If is acknowledged that there are many circumstances that require applicants to have other parties interact with the OGD on their behalf relative to specific applications. Frequently, written authorization for these agents is not contained in an application when submitted. The Office wishes to be cooperative in its response to applicant needs but must assure submitted material remains confidential and is not released or discussed with unauthorized individuals.

In order to allow for prompt responses, it is requested that written authorization be submitted to the application when filed or well before contact by an authorized agent is expected. Examples of who requires such authorization include:

A. The U.S. agent of a foreign firm.

B. A consultant to the firm that is expected to interact directly with OGD.

C. Legal counsel to the firm on issues that may necessitate direct interaction with OGD.

INFORMATION FOR INSPECTIONS

United States agents for foreign establishments are very helpful to the Office of Compliance in assigning foreign inspections. It is, therefore, important that complete information (name, address, phone/fax numbers) of the U.S. agent be included in an application.

Central File Numbers (CFN) as identifiers for facilities are also of value in the scheduling of inspections. Please provide these numbers for all facilities included in the application. CFN's are

obtained by applying for them through the FDA District Offices.

OTHER

WITHDRAWAL OF APPLICATION

The Office requests that firms make periodic internal assessments and withdraw pending applications they may not wish to pursue to approval. This action will allow conservation of OGD's information tracking and document control resources.

Guidance for Industry

Revising ANDA Labeling Following Revision of the RLD Labeling

U.S. Department of Health and Human Services Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2000
OGD

Guidance for Industry Revising ANDA Labeling Following Revision of the RLD Labeling

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

(Internet)
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2000
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Guidance for Industry[1]

Revising ANDA Labeling Following Revision of the RLD Labeling

I. INTRODUCTION

This guidance is intended to assist sponsors of abbreviated new drug applications (ANDAs) in deciding when and how to submit labeling supplements following labeling revisions to their reference listed drugs (RLDs).

II. BACKGROUND

During the marketing life of a drug product approved under a new drug application (NDA), the package insert labeling is frequently revised. When an NDA serves as an RLD for an ANDA, approved changes in the RLD labeling generally necessitate changes in the labeling of one or more ANDAs using the RLD. Under the Federal Food, Drug, and Cosmetic Act and Agency regulations, an ANDA product must have the same labeling as the RLD.

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[1] This guidance has been prepared by the Office of Generic Drugs in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration. This guidance document represents the Agency's current thinking on changes in labeling of approved abbreviated new drug applications (ANDAs) following revisions in the RLD's labeling. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulation, or both.

Section 505(j)(2)(A)(v) of the Act states that an abbreviated application for a new drug must contain

> information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug ... except for changes required because of differences approved under a petition ... or because the new drug and the listed drug are produced or distributed by different manufacturers.

Similar statements are also found in the regulations at 21 CFR 314.94(a)(8)(iv).

Previously, OGD notified the appropriate ANDA sponsors when the approved labeling of their RLD changed. This was usually done using a formal supplement request letter. In cases where an NDA served as the RLD for multiple generic products, the preparation of a large number of request letters took a significant amount of review staff time. With the increase in the numbers of approved NDAs and ANDAs, this approach was using an increasingly disproportionate share of OGD's resources. Because of the time it took, the approach sometimes even delayed the notification of ANDA sponsors. With the exception of a few special situations (noted below), ***OGD is no longer providing this type of notification***. The sponsor of an ANDA is now responsible for ensuring that the labeling contained in its application is *the same as* the currently approved labeling of the RLD. OGD has determined that this change in responsibility is necessary to minimize the implementation time for the introduction of revised labeling into the market place. OGD believes that prompt revision, submission to the Agency, and

implementation of revised labeling are important to ensure the continued safe and effective use of generic drug products. Because the regulations state that the labeling of the generic must be the same as the innovator, the revision should be made at the very earliest time possible. If there is any potential delay in the revision of a generic drug labeling, the sponsor should contact OGD.

III. HOW TO OBTAIN INFORMATION ON A CHANGE IN RLD LABELING

The sponsor of an ANDA should routinely monitor the Labeling Review Branch Homepage (see below) for information on changes in labeling. OGD's Labeling Review Branch will:

- Place monthly updates of approved labeling changes for RLDs with approved ANDAs on the Labeling Review Branch Homepage at:

http://www.fda.gov/cder/ogd/rld/labelingreviewbranch.html

Continue to notify ANDA applicants by facsimile, telephone, and/or letter for any labeling revision approved for the RLD that warrants ***immediate*** widespread professional notification, such as those changes connected to issuing a *Dear Doctor Letter* or similar significant changes.

All approved labeling for RLDs is still available from Freedom of Information Staff. Sponsors who wish to obtain labeling using this mechanism should send a written or facsimile request to:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-827-6500; FAX: 301-443-1726

When a labeling revision is needed, the ANDA sponsor should take appropriate action to revise the ANDA labeling and submit the revised labeling to the FDA.

IV. HOW TO SUBMIT REVISED LABELING

All ANDA labeling changes needed because of approved changes to the labeling of the RLD may be submitted as a *Special Supplement - Changes Being Effected.* Such supplements should include:

- 12 copies of final printed labeling
- the date the revised labeling will be used (go into effect)
- a side-by-side comparison of the ANDA labeling with the approved labeling of the RLD with all differences annotated and explained, as described in 21 CFR 314.94(a)(8)(iv)

Sponsors should contact the OGD Labeling Review Branch at 301-827-5846 if there are any questions about the information in this guidance.